REMARKS

Claims 45, 49, 56, and 58 have been amended. Claims 1-62 are pending in the instant application. Support for the amendments to the claims can be found in the specification at, for example, page 65, lines 17-28 and page 54, lines 20-23. No new matter has been added as a result of the above-described amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

1. Advisory Information

The Examiner notes in the instant Office Action that Applicants may have mistakenly inserted claim number 34 in claim 45 in place of another claim number. Applicants wish to thank the Examiner for this observation, and have amended claim 45 so that it refers back to claims 15 or 23, rather than to claims 15 or 34.

2. Information Disclosure Statement

The Office Action states that certain references listed on the Information Disclosure Statement filed July 27, 2001 were not present, and therefore, have not been considered. Applicants hereby file a Supplemental Information Disclosure Statement listing those references that, due to inadvertent errors or omissions in the Information Disclosure Statement filed July 27, 2001, have not yet been considered. In addition, the Supplemental Information Disclosure Statement lists one reference that was not available at the time the prior Information Disclosure Statement was filed.

3. Objection to the specification

The Office Action contains an objection to the specification because the references to "Figures 6A-6B" and "Figure 7" at pages 6-7 do not match the figures. Applicants have amended the specification so that the references to these figures at pages 6-7 match the figures, and, therefore, respectfully request that this objection be withdrawn.

4. Objection to claim 49 under 37 C.F.R. § 1.75(c)

The Office Action contains an objection to claim 49 under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. The

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Action states that the phrase "the nucleic acid molecule defined in Claim 1" is unclear. Applicants have amended claim 49 to recite instead "the nucleic acid molecule of Claim 1." Applicants contend that the claim 49, as amended, complies with 37 C.F.R. § 1.75(c), and therefore, respectfully request that this ground of rejection be withdrawn.

5. Claim of priority

The Office Action asserts that the amino acid sequences set forth in SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, and SEQ ID NO: 20 are entitled under 35 U.S.C. § 119(a) to the benefit of the June 21, 1989 filing date of German Patent Application No. P39 20 282.8. The Action also asserts that the amino acid sequence set forth in SEQ ID NO: 2 is entitled under 35 U.S.C. § 119(a) to the benefit of the April 6, 1990 filing date of European Patent Application No. 90106624.1.

Although Applicants respectfully disagree with each of the Action's priority determinations, Applicants contend that neither determination is relevant to the rejections made in the instant Action (*see* discussion in sections 9 and 10 below). Applicants, therefore, acknowledge the Action's priority determinations, and elect to address these determinations when either determination becomes relevant to the patentability of the instant claims.

6. Provisional rejection of claims 1-62 on obviousness-type double patenting grounds

The Office Action provisionally rejects claims 1-62 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-59 of co-pending Application No. 09/899,429 (the '429 application). The Action states that because the claims of the '429 application recite the limitation "wherein said polypeptide is not associated with human urinary proteins," the claims of the instant application and the '429 application are not identical. The Action also states, however, that although the instant application and the '429 application are not identical, the claims of the instant application are not patentably distinct from the claims of the '429 application because this limitation is not a true limitation, since the proteins in both applications are recombinantly produced and would, therefore, not be associated with human urinary proteins.

Applicants respectfully disagree with the Action's assertion that since the proteins in both the instant application and the '429 application are recombinantly produced, they could not also be

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associated with human urinary proteins. However, because the instant Action has asserted only a provisional rejection of claims 1-62 under the doctrine of obviousness-type double patenting, Applicants elect to address this ground of rejection by submitting a Terminal Disclaimer or by argument upon notification that this rejection has been made non-provisional, all other conditions for patentability have been met, and the instant claims are otherwise in condition for allowance.

7. Rejections of claims 15-22 and 45-62 under 35 U.S.C. § 112, second paragraph

The Office Action asserts a rejection of claims 15-22 and 45-62 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Office Action asserts a rejection of claims 15-22, 45-48, and 50-62 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Action states that claims 15-22, 45-48, and 50-62 are indefinite because the phrase "at least one" in claim 15 does not put an upper limit on the extent of the changes to be made.

Applicants respectfully disagree with the assertion that claims 15-22, 45-48, and 50-62 are indefinite. Applicants contend that claim 15, from which claims 16-22, 45,-48, and 50-62 refer, contains an explicit limitation to encompass only those molecules that possess a particular activity, namely, the *ability to bind TNF*. The specification defines the "ability to bind TNF" as "the ability of a protein to bind to TNF-α in such a way that TNF-α is prevented from binding to the functional part of the receptor and the activity of TNF-α in humans or animals is inhibited or prevented altogether" (page 17, lines 23-28). Applicants respectfully disagree with the assertion made in the instant Action regarding the specie of substituted molecule having conservative substitutions at every amino acid position. The Action asserts that such a molecule could be made without destroying the ability of the resulting variant to bind TNF-α in such a way that TNF-α is prevented from binding to the functional part of the receptor and the activity of TNF-α in humans or animals is inhibited or prevented altogether. Applicants respectfully disagree, and request any reference or other information known to the Patent Office to support the position that *every* amino acid of the disclosed sequences could be conservatively substituted and *still* bind TNF-α. Applicants contend that they are under no duty to define, with absolute precision, the number of modifications that would be tolerable

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without destroying the ability of a molecule to bind TNF. Applicants also contend that the requirements of 35 U.S.C. § 112, second paragraph, are met because one of ordinary skill in the art would readily recognize that a molecule having conservative substitutions at *every* amino acid position would lack high affinity TNF-α binding activity. Moreover, Applicants contend that 35 U.S.C. § 112, second paragraph, only requires that one of ordinary skill in the art would be able to determine which species fall within the scope of the claim (for example, by using the teachings of the specification at, *inter alia*, page 16, lines 28-31) in order for the claim language to be definite. Applicants, therefore, contend that claims 15-22, 45-48, and 50-62 satisfy the definiteness requirement of § 112, second paragraph, and respectfully request that this ground of rejection be withdrawn.

The Action also asserts that claim 49 is indefinite for reciting "[a] nucleic acid that hybridizes under moderately or highly stringent conditions," because the specification does not define any hybridization conditions, and the term "moderately or highly stringent" does not clearly set forth the metes and bounds of the patent protection desired.

Applicants respectfully disagree with the assertion that the specification does not define any hybridization conditions. In fact, the specification discloses that cDNA clones containing TNF binding protein coding sequences were isolated from a fibrosarcoma cDNA library by hybridization for 16 hours at 65°C using a 0.4 kb probe isolated from the TNF-α induced fibrosarcoma cDNA library in a hybridization solution composed of 6x SSC, 5X Denhardt's, and 0.1% SDS (page 65, lines 17-28; page 54, lines 20-23). However, in an effort to expedite prosecution of the instant application, Applicants have amended claim 49 to recite "[a] nucleic acid that hybridizes to the complement of the nucleic acid molecule of Claim 40 at 65°C in a hybridization buffer comprising 6x SSC, 5 X Denhardt's, and 0.1% SDS." Applicants contend that amended claim 49 satisfies the definiteness requirement of § 112, second paragraph, and therefore, respectfully request that this ground of rejection be withdrawn.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, second paragraph, have been overcome by amendment or traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

8. Rejections of claims 15-22, 37-40, 43-48, and 50-62 under 35 U.S.C. § 112, first

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paragraph

The Office Action asserts a rejection of claims 15-22, 37-40, 43-48, and 50-62 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. The Action states that the specification, while being enabling for making and using a polypeptide comprising the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, or SEQ ID NO: 20, does not reasonably provide enablement for making and using recombinant polypeptide variants of these sequences having at least one conservative amino acid substitution, at least one amino acid substitution at a glycosylation site, at least one amino acid substitution at a proteolytic cleavage site, at least one amino acid substitution at a cysteine residue, at least one amino acid deletion, at least one amino acid insertion, or a combination of these modifications. The Action also states that in the absence of information concerning those residues in the amino acid sequence of SEQ ID NO: 4 that are essential for its biological activity and structural integrity, a person skilled in the art would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional, and substitutional mutation analysis before that person could begin to rationally design a functional TNF binding protein variant.

The Action also asserts a rejection of the claims under 35 U.S.C. § 112, first paragraph, in so far as the claims encompass an isolated protein other than a recombinant polypeptide comprising the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, or SEQ ID NO: 20, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Action states that because the specification merely discloses one polypeptide sequence, the written description does not support the claimed scope and does not fulfill the written description requirements of 35 U.S.C. § 112, first paragraph.

Applicants respectfully disagree with the assertion that the specification does not enable a skilled artisan to use the invention commensurate in scope with the claims, or that that the specification fails to reasonably convey to a skilled artisan that the inventors had possession of the claimed invention at the time the application was filed. Applicants note that the specification sets

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forth the amino acid sequences of a TNF receptor polypeptide (page 5, lines 7-39) and a 161 amino acid portion of this sequence having the ability to bind TNF (page 5, line 45 to page 6, line 3). The specification also discloses that the first 29 amino acid residues of the TNF receptor polypeptide constitute the signal peptide (page 21, line 35 to page 22, line 2), and that amino acid residues 30-40 and 202-211 are proteolytically cleaved from the TNF receptor to form the TNF binding protein (page 22, lines 11-12 and page 23, lines 27-29). The specification teaches that techniques for making conservative substitutions are well known in the art (page 14, lines 13-15), and provides a list of exemplary conservative substitutions (page 15, Table 1). Applicants contend that they are under no duty under the statute to enumerate all of the species disclosed generically in their specification, particularly where, as here, the structure of the native molecule is disclosed, the types of variants of said structure are generically disclosed, and a functional property of the claimed molecule (TNF binding activity) as well as assays to assess species for said property are disclosed. The specification further teaches the location of glycosylation sites (page 22, lines 16-19), proteolytic cleavage sites (page 22, lines 26-28 and page 23, lines 27-29), and cysteine residues (SEQ ID NO: 2), wherein amino acid substitutions can be made.

Applicants also respectfully disagree with the Action's assertion that the claims of the instant application are analogous to claim 7 of U.S. Patent No. 4,703,008 (the '008 patent), which was held invalid for lack of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). In that case, the Federal Circuit did not set forth a *per se* rule that claims to substitution and other variants of disclosed nucleotide or amino acid sequences were invalid or required explicit support for each and every claimed species. Rather, the Court noted that for inventions directed to DNA sequences, the specification must disclose how to make and use enough sequences to justify the grant of the claims sought in order to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. *Amgen Inc.*, 927 F.2d at 1213. The Court determined that the specification of the '008 patent was insufficient to enable one of ordinary skill in the art to make and use the claimed invention because it disclosed how to make and use only a few of the nearly infinite number of erythropoietin variants encompassed by claim 7 and little or no information on structural features of the EPO molecule important for red blood cell producing activity (in addition, the trial court had found that a skilled artisan, by making substitutions at only three positions in the erythropoietin sequence, could generate over a million different erythropoietin

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variants). *Id.* Because the disclosure was limited to only a few erythropoietin variants, the specification failed to disclose how to make and use enough sequences to justify a claim encompassing *any* DNA sequence that encodes a polypeptide having erythropoietin-like activity. *Amgen Inc.*, 927 F.2d at 1213-14. In stark contrast, the instant application discloses, for example, the metes and bounds of a 161 amino acid portion of the TNF receptor polypeptide wherein resides the molecule's ability to bind TNF; the locations of glycosylation sites, proteolytic cleavage sites, and cysteine residues; and a list of exemplary conservative substitutions. In addition, the claims of the instant application are not directed to methods that use *any* DNA sequence that encodes a polypeptide having the ability to bind TNF, but rather are directed to methods that use sequences which are closely related to the disclosed TNF binding sequences of the invention. Applicants respectfully contend that because the specification discloses how to make and use enough sequences and enables one skilled in the art to carry out the invention commensurate with the scope of the claims, the claims of the instant application are not analogous to claim 7 of the '008 patent and hence not invalid for non-enablement.

Applicants also note that independent claims 1, 14, 15, 23, 36, 37, 41-44, and 49 contain an explicit limitation to encompass only those molecules that possess a particular activity, namely, the *ability to bind TNF*. The specification defines the "ability to bind TNF" as "the ability of a protein to bind to TNF-α in such a way that TNF-α is prevented from binding to the functional part of the receptor and the activity of TNF-α in humans or animals is inhibited or prevented altogether" (page 17, lines 23-28). In view of the explicit limitation that the claimed molecules possess the ability to bind TNF, Applicants also respectfully disagree with the Action's assertion regarding the specie of substituted molecule having conservative substitutions at every amino acid position. The Action asserts that by making conservative amino acid substitutions at every residue, one of ordinary skill in the art can prepare a polypeptide comprising an amino acid sequence that completely differs from the polypeptides disclosed in the instant specification and expect it to have the same functions as the polypeptides disclosed in the instant specification. Applicants contend that one of ordinary skill in the art would appreciate that a polypeptide prepared by making conservative amino acid substitutions at every residue would not have the same functions as the unsubstituted polypeptide, and ask the Patent Office to supply any reference or other information supporting a contrary view. Applicants contend that in view of the instant specification's teachings (as discussed above), one of ordinary

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skill in the art would readily be able to determine which TNF binding protein variants have the ability to bind TNF, and therefore, that it would not require undue experimentation for one of ordinary skill in the art to determine which TNF binding protein variants fall within the scope of the instant claims.

Applicants contend that the specification conveys to one of ordinary skill in the art that the inventors had possession of the claimed invention, and therefore, respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

9. Rejection of claims 15, 22, 37-40, and 43-49 under 35 U.S.C. § 102

The Office Action asserts a rejection of claims 15, 22, 37-40, and 43-49 under 35 U.S.C. § 102(a) as being anticipated by European Patent Application No. 0 308 378 (Wallach *et al.*, published March 22, 1989), contending that this reference discloses the purification of a TNF-inhibiting protein that the instant specification describes as being identical to a TNF binding protein of the instant invention. The Action states that while the amino acid sequences set forth in SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, and SEQ ID NO: 20 comprise up to 21 more amino acid residues than the soluble TNF binding protein of Wallach *et al.*, this reference encompasses a TNF binding protein of the instant invention comprising a C-terminal deletion. The Action also states that while the amino acid sequences set forth in SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, and SEQ ID NO: 20 are not taught by Wallach *et al.*, the amino acid sequence of a protein is an intrinsic property of the protein. The Action further states that the Wallach *et al.* reference discloses that TNF binding proteins may be used in treating any condition where there is an over-production of endogenous TNF, such as in cases of septic shock, cachexia, graft-versus-host reactions, and autoimmune diseases like rheumatoid arthritis. Applicants respectfully traverse this rejection.

To support a rejection under 35 U.S.C. § 102, "the four corners of a single, prior art document [must] describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994). The exclusion of even a single claimed element from a reference, no matter how insubstantial or obvious, is enough to negate

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anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. (BNA) 193, 198 (Fed. Cir. 1983). The identical invention must also be shown in the single prior art reference in as complete detail as contained in the application against which the reference is cited. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Moreover, the prior art reference must be enabling, thus placing the claimed invention in the possession of the public. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 88 (D. Mass 2001) (citing *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986)).

Applicants note that European Patent Application No. 0 308 378 provides only a *partial, incomplete* amino acid sequence of a TNF inhibitory protein – and no nucleotide sequence whatsoever (*see* page 3, line 61; page 8, line 21; and page 9, line 33). Applicants contend that because the Wallach *et al.* reference does not disclose the complete nucleotide and amino acid sequence of TNF binding protein in EP 0 308 378 – and in fact, discloses *only* fourteen of the first sixteen amino acid residues of a TNF inhibitory protein – this reference *cannot* anticipate methods for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a recombinant polypeptide having the ability to bind TNF, wherein said polypeptide comprises the amino acid sequence as set forth in any of SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, residues 2 through 183 of SEQ ID NO: 10, residues 2 through 173 of SEQ ID NO: 16, or residues 2 through 172 of SEQ ID NO: 20. There is no evidence in the Wallach *et al.* reference that the small fragment for which sequence has been disclosed has the ability to bind TNF, a recited limitation of the instantly-claimed peptides and proteins. The lack of such evidence in the reference precludes application of the Wallach *et al.* reference in support of the asserted anticipation rejection.

Applicants also note that the Wallach *et al.* reference discloses a TNF binding protein purified from human urine by use of dialysis, ion exchange chromatography, and reverse phase high pressure liquid chromatography. Applicants contend that because the TNF binding protein disclosed by Wallach *et al.* is purified from urine, this reference *cannot* anticipate methods that use a *recombinant* polypeptide having the ability to bind TNF. Only Applicants' invention provided the nucleic acid sequence of TNF binding protein, which was absolutely necessary, in order to recombinantly produce TNF binding protein (page 19, line 30 to page 20, line 2). Moreover,

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Applicants contend that the assertion that methods that use a purified TNF binding protein anticipate methods that use a recombinant TNF binding protein is entirely analogous to the assertion, made in *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, that erythropoietin purified from patients with anemia anticipates recombinant erythropoietin. 126 F. Supp. 2d 69, 88 (D. Mass 2001) (holding that a reference disclosing erythropoietin purified from patients with anemia does *not* anticipate claims to recombinant erythropoietin).

Applicants contend that European Patent Application No. 0 308 378 cannot anticipate the claimed methods of the present application, and therefore, respectfully request that the rejection of claims 15, 22, 37-40, and 43-49 on 35 U.S.C. § 102 grounds be withdrawn.

10. Rejection of claims 15 and 22 under 35 U.S.C. § 103

The Office Action asserts a rejection of claims 15 and 22 under 35 U.S.C. § 103(a) as being unpatentable over Olsson *et al.*, 1989, *Eur. J. Haematol.* 42:270-75, and further in view of European Patent Application No. 0 308 378 (Wallach *et al.*, published March 22, 1989). The Action states that because the Olsson *et al.* reference discloses the isolation of a TNF binding protein comprising an amino-terminal sequence (*i.e.*, Asp-Ser-Val-Xaa-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-Val-Asn-Ser-Ile-Xaa-Lys-Thr) that differs from the amino acid sequence set forth in SEQ ID NO: 2 at only two positions, this reference encompasses a TNF binding protein of the instant invention comprising at least one amino acid substitution and a C-terminal deletion. The Action also states that while the Olsson *et al.* reference does not disclose a method of treatment comprising administering a TNF binding protein of the instant invention, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the TNF binding protein disclosed in the Olsson *et al.* reference to treat the TNF-mediated disorders disclosed in the Wallach *et al.* reference. Applicants respectfully traverse this rejection.

The claims of the instant application recite methods for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a *recombinant* polypeptide having the ability to bind TNF. Applicants note that the Olsson *et al.* reference discloses a TNF binding protein purified from the urine of patients with chronic renal failure by use of ion exchange chromatography, affinity chromatography on TNF-Sepharose, and reverse phase chromatography. Applicants contend that because the TNF binding

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protein disclosed by Olsson *et al.* is purified from urine, this reference does *not* teach a *recombinant* polypeptide having the ability to bind TNF. Only Applicants' invention provided the nucleic acid sequence of TNF binding protein, which is absolutely necessary to recombinantly produce TNF binding protein (page 19, line 30 to page 20, line 2). Applicants also note that the Olsson *et al.* reference does not disclose the complete nucleotide and amino acid sequence of TNF binding protein – and in fact, discloses *only* eighteen of the first twenty amino acid residues of a TNF inhibitory protein. Applicants contend that it would not have been *prima facie* obvious to one of ordinary skill in the art to use the TNF binding protein disclosed by Olsson *et al.*, and purified from urine, to practice the claimed methods of the invention using a recombinant polypeptide having the ability to bind TNF. Applicants, therefore respectfully request that the rejection of claims 15 and 22 on 35 U.S.C. § 103 grounds be withdrawn.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner O'Hara believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Dated: July 29, 2003

By: _____
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